Docket No. 96700/733

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Name: Elie H. Gendloff
Signature:

Applicant	:	Tamar H. Michaeli
Serial No.	:	Unknown
Filed	:	February 27, 2002 (herewith)
For	:	A METHOD OF IDENTIFICATION OF INHIBITORS OF PDE1C AND METHOD OF TREATMENT OF DIABETES
Examiner	:	Unknown
Group Art Unit	:	Unknown

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

This Preliminary Amendment accompanies the filing of a continuation application of U.S. Patent Application 09/245,169. A copy of the 09/245,169 application as filed is enclosed herewith. Also enclosed is a copy of the Declaration and the Small Entity Statement filed in the 09/245,169 case. The small entity status is currently valid for this continuation application.

Sequence Listing

Also enclosed herewith is a copy of the Sequence Listing filed in the 09/245,169 case. Pursuant to 37 CFR 1.821(e), please use the computer readable Sequence Listing that is already on file in U.S. Patent Application 09/245,169. The enclosed paper copy of the Sequence Listing is identical to the computer readable copy on file in U.S. Patent Application 09/245,169.

Information Disclosure Statement

Also enclosed herewith is an Information Disclosure Statement that has been previously filed and considered in the parent application, U.S. Patent Application 09/245,169. Pursuant to MPEP 609 I.A.2., applicant requests that these references be considered in the instant application.

Formal Drawings

The drawings enclosed herewith are considered by the applicant to be formal drawings. Applicant thus requests review and approval of the drawings by a Draftsperson.

Amendments

Please enter the following amendments in this case.

IN THE SPECIFICATION

On page 1, before the Statement of Goverment Interest, please add the following.

--This application is a continuation of U.S. Patent Application 09/245,169, filed February 5, 1999.--

On page 14, please replace the paragraph on lines 7-11 with the following:

--Figure 5. Figure 5 depicts the DNA sequence of a PDE1C cDNA (SEQ ID NO:1) that confirms that PDE1C is expressed in pancreatic islet ß-cells. Reverse transcriptase polymerase chain reaction was used to amplify and clone a fragment of the PDE1C mRNA common to all known PDE1C isozymes.--

Page 26, line 7 to page 27, line 1, after "early passages" and before "were maintained" delete the citation to references "(Grodsky, G.M. and Bolaffi, J. L. (1992) . . . *J. Biol. Chem.* 272, 16152-16157)".

On page 28, please replace the two paragraphs on lines 10-25 with the following:

--Reverse transcriptase polymerase chain reaction (RT-PCR) analysis. RT-PCR analysis was performed on 5 μg of RNA prepared from ßTC3 cells using Trizol (Gibco-BRL). Controls lacking reverse transcriptase were included in the reactions. To determine expression of PDE1C the following oligonucleotides were used: for RT - oligo dT; and for PCR amplification - JWPDE1C-5 5'-ACAGGGCAGAGGAGATCAAGTTT (SEQ ID NO:2); and JWPDE1C-3 5'-CTTTTCGCCTGCCTTTTCTCCTT (SEQ ID NO:3). The 408 bp PCR product was cloned and its DNA sequence was determined.

The following oligonucleotides were used for PCR amplification to determine the expression of PDE4A: JWPDE4A-5 5'-AGCCATGGAACAGTCAAAGGTCAA (SEQ ID NO:4); and JWPDE4A-3 5'-TCAGGAGGGCCAGGAGTCGT (SEQ ID NO:5); and to determine the expression of PDE4D: JWPDE4D-5 5'-GAGGGCCGGCAGGGACAGAC (SEQ ID NO:6); and JWPDE4D-3 5'-GGGGGTGGGGTGGGTGAGAGG (SEQ ID NO:7). Amplification products 436 AND 470 bp long were obtained for PDE4A and D, respectively.--

IN THE CLAIMS

Please cancel claims 1-9 and enter the following claims 10-19.

10. A method of increasing glucose dependent insulin secretion in a pancreatic β-cell in a mammal, the method comprising treating the β-cell with an inhibitor of

phosphodiesterase 1C.

11. The method of claim 10, wherein the inhibitor is an isobutylmethylxanthine derivative with substitutions at positions 2 (R1) and 8 (R2).

12. The method of claim 11, wherein R1 and R2 are independently a moiety selected from the group consisting of an alkyl (C_1 to C_3), a flouroalkyl (F_1 to F_3), a chloroalkyl (Cl_1 to Cl_3), an aryl (C_5 to C_6), a fluoroaryl (F_1 to F_2), and a chloroaryl (Cl_1 to Cl_2).

13. The method of claim 10, wherein the inhibitor is selected from the group consisting of IBMX, zaprinast, 8-methoxymethyl-1-methyl-3-(2-methylpropyl)xanthine (8MM-IBMX), and combinations thereof.

14. The method of claim 13, wherein the inhibitor is zaprinast.

15. The method of claim 13, wherein the inhibitor is 8-methoxymethyl-1-methyl-3-(2-methylpropyl)xanthine (8MM-IBMX).

16. The method of claim 10, wherein the mammal is a human.

17. The method of claim 10, wherein the inhibitor is administered in an amount effective to regulate blood sugar levels in the mammal.

18. The method of claim 10, wherein the inhibitor is administered orally.

19. The method of claim 10, wherein the inhibitor is administered in combination with an anti-diabetic agent selected from the group consisting of insulin, a sulfonylurea, and a biguanide.

Remarks

Applicant has entered specification amendments that provide priority information or that were previously entered in the parent case. Applicant has also amended the claims to be directed to methods of increasing glucose dependent insulin secretion in a pancreatic β-cell in mammals. Applicant asserts that the new claims are fully supported in the specification as filed.

Support for claim 10 is found at least in the Experimental Details section, at pages 25-47.

Support for claim 11 is found at least at page 19, line 25 to page 20 line 4.

Support for claim 12 is found at least at page 11, lines 10-18.

Support for claims 13-15 is found in the Experimental Details section, at pages 25-47.

Support for claim 16 is found at least at page 20, lines 11-27.

Support for claim 17 is found at least in the originally filed claims.

Support for claim 18 is found at least at page 21, line 22 to page 22, line 13.

Finally, support for claim 19 is found at least at page 24, line 17 to page 25, line 3.

Conclusion

Applicant requests examination of the claims as amended. Should there be any minor matters preventing such examination, applicant requests that the Examiner contact the attorney indicated below.

Respectfully submitted,

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Dated: New York, New York
February 27, 2002

By: _____
Elie H. Gendloff
Registration No.: 44,704

Appendix
Marked up amendments
Continuation of U.S. Patent Application 09/245,169, Filed February 27, 2002
Added material is underlined; deleted material is bracketed.

In the Specification:

On page 14, the paragraph on lines 7-11 has been amended as follows:

Figure 5. Figure 5 depicts the DNA sequence of a PDE1C cDNA (SEQ ID NO:1) that confirms that PDE1C is expressed in pancreatic islet ß-cells. Reverse transcriptase polymerase chain reaction was used to amplify and clone a fragment of the PDE1C mRNA common to all known PDE1C isozymes.

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